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EXAMINER	
MYERS, CARLA J	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/826,522	DEPHILLIPO ET AL.	
	Examiner	Art Unit	
	Carla Myers	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *21 July 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *105 and 110-112* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *105,110- 112* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/1/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to the amendment filed July 21, 2008. Applicant's arguments have been fully considered but are not persuasive to overcome all grounds of rejection. All rejections not reiterated herein are hereby withdrawn. In particular, the previous rejection of claim 105 under 35 U.S.C. 112, second paragraph has been obviated by the amendments to the claim.

This action contains new grounds of rejection necessitated by Applicant's amendments to the claims and is made final.

2. Claims 105 and 110-112 are pending and have been examined herein.

Election/Restrictions

3. Applicant's election with traverse of Group 3 (the combination of the polymorphism in the catalase gene and the CuZnSOD gene) in the reply filed on July 21, 2008 is acknowledged. The traversal is on the ground(s) that inventions I-IV (as set forth in the Office action of June 20, 2008) fall within class 435, subclass 6. It is asserted that it would not require undue burden to examine each of inventions I-IV together.

This is not found persuasive because it is maintained that undue burden would be required to examine invention III together with inventions I, II and IV, since each of the inventions requires distinct searches that are not co-extensive with one another. The different inventions require the search of polymorphisms which occur in different genes. The polymorphisms thereby have different structural features, with respect to their nucleotide or amino acid identity and location. Further, the polymorphisms have

different functions and effects. Accordingly, the polymorphisms do not share both a common structure and effect, as is required to show that they are of a similar nature. A search for each of the genes and their polymorphisms requires a different keyword and polymorphism search. For instance, a search for polymorphisms in a CuZnSOD gene would not lead one to all references teaching polymorphisms in the MnSOD gene. Additionally, a finding that the detection of polymorphisms in one of the genes, e.g., CuZnSOD, is anticipated or rendered obvious by the prior art would not necessarily extend to a finding that detection of a polymorphism in a MNSOD gene is also anticipated or rendered obvious by the prior art. Accordingly, it is maintained that undue burden would be required to examine each of the inventions together.

The requirement is still deemed proper and is therefore made FINAL.

Declaration

4. The Declaration under 37 CFR 1.132 filed April 30, 2007 is insufficient to overcome the rejection of claims 105 (and newly added claims 110-112) based upon 35 USC 112 first paragraph as set forth in the last Office action for the reasons discussed in detail in paragraph 5 below.

Claim Rejections - 35 USC § 112 first paragraph - Enablement

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 105 and 110-112 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter

which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

This rejection was previously presented in the Office action of June 3, 2005 and has been modified herein to address Applicant's amendments to the claims.

The following factors have been considered in formulating this rejection (*In re Wands*, 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

Breadth of the Claims:

Claim 105 is broadly drawn to a method for selecting a dose of an anti-oxidant composition for administration to a human wherein the method comprises assessing the occurrence of a polymorphism at position -262 of a catalase gene and a polymorphism resulting in a val to glu substitution at amino acid position 7 of Cu/Zn superoxide dismutase (CuZnSOD). The claims recite that it is a property of any oxidative damage-associated polymorphism that it indicates an increased susceptibility to any pathology involving oxidative damage. The claims do not set forth the identity of the polymorphism, and thereby recite the property of any polymorphism undefined in terms of its chemical structure (e.g., nucleotide position, nucleotide identity and gene in which the polymorphism is located).

Claim 110 further recites a step of assessing the degree to which a human is susceptible to any undesirable oxidative stress disorder-associated by detecting any polymorphism in any catalase or superoxide dismutase gene and summing the number of any polymorphism or assigning a weighting factor to any polymorphism and thereby assessing the susceptibility to any oxidative stress condition. Again, the polymorphisms in the catalase and SOD genes are not defined in terms of any particular structural features, such as their nucleotide position or identity. The number of polymorphisms that are summed are also not defined in terms of any structural properties, such as the genes in which they occur, their nucleotide position or their nucleotide identity.

The claims include the detection of any of a multitude of polymorphisms that are in some manner associated with any oxidative stress condition.

While the claims do not specify the particular polymorphism (i.e., the nucleotide position and identity of the polymorphism), SOD and catalase genes are known to contain a multitude of polymorphisms, potentially associated with some disease. For instance, the SOD1 gene contains at least 42 distinct polymorphisms, SOD2 contains at least 135 polymorphisms, the SOD3 gene contains at least 63 polymorphisms, the CAT gene contains at least 136 polymorphisms, and the TYRP1 (catalase B) gene contains at least 65 polymorphisms (see BIOINFO gene card printouts from Weizmann Institute of Science).

Nature of the Invention

The claims encompasses methods for determining the dosage of an antioxidant by detecting the presence of a nucleotide variation. The invention is in a class of

inventions which the CAFC has characterized as 'the unpredictable arts such as chemistry and biology" (Mycolgen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Federal Circuit 2001)).

Teachings in the Specification and State of the Art:

The specification outlines a method for determining the dose of an antioxidant to be given to a human patient that has polymorphisms in genes which encode for proteins associated with conversion of toxic oxygen to less toxic oxygen species, genes which encode for proteins which protect against oxidative stress, genes which encode for proteins that produce toxic oxygen species, genes which code for proteins that indirectly affect oxidative stress, and genes which encode for proteins which alter the level of expression of a protein associated with oxidative stress (see page 3). The specification states that the occurrence of any one polymorphism in any one of these gene types means that the individual will be more susceptible to oxidative damage as compared to an individual who does not have the polymorphism, and that the occurrence of a plurality of polymorphisms indicates an even higher susceptibility to oxidative damage. It is further stated (page 5) that a dosage of an antioxidant can be selected based on an assessment of disorder-associated polymorphisms. At page 6, the specification teaches that the polymorphisms may be assessed by determining the number of polymorphisms presented. Alternatively, weighing factors can be assigned to each polymorphism and the sum of the weighing factors is determined to yield a value that represents the relative susceptibility damage. Additionally, the specification (pages 12-13) discloses a number of genes associated directly or indirectly with protecting against oxidative

damage which contain particular polymorphisms that have been shown in the prior art to be associated with disorders. In particular, the specification teaches the polymorphisms of a valine amino acid substitution at position 9 of the MnSOD protein, a polymorphism which results in the presence of an isoleucine at amino acid 58 of MnSOD, a polymorphism which results in a valine to glutamic acid substitution at amino acid 7 of CZSOD, a polymorphism which leads to a cysteine to phenylalanine substitution at amino acid 6 of CZSOD, and a polymorphism which leads to a cytosine to thymine substitution at nucleotide –262 of the catalase gene promoter. It is stated that polymorphisms in the MnSOD, CZSOD, CAT and GP genes are of more significance than polymorphisms in other genes and that preferably these genes are given a weighing factor that is twice that assigned to other genes (see page 15). It is also taught that the significance of a polymorphism may be influenced by its association with a disorder and that this should be taken into consideration when weighing the polymorphisms' significance. General methods are taught whereby one may calculate a susceptibility score if the number of affected individuals in a population having the polymorphism is known (pages 15-16). If the significance and correlation factors are not known, then the value of 1.00 can be assigned to any polymorphism.

Working Examples:

The specification does not exemplify methods in which the dosage of an antioxidant composition is selected based on an assessment of an individuals polymorphisms. The specification teaches polymorphisms that have been disclosed in the prior art and teaches a means for calculating the weighing factor for a MnSOD mutation based on

data provided in the prior art (Kimura et al) which teaches the odds ratio of the MnSOD mutation. However, the specification does not teach how this information is taken together with information related to mutations in the catalase gene in order to calculate the quantity of antioxidant that should be given to an individual. Thereby, while the specification and prior art set forth the general concept that mutations in genes which normally protect against oxidative stress, may cause an increase in susceptibility to oxidative damage and that anti-oxidants may counteract this effect, the specification does not exemplify how modification of the dose of an antioxidant based on the quantity of polymorphisms will effect the occurrence or outcome of a disease, or any other parameter associated with the disease.

The Predictability or Unpredictability of the Art and Degree of Experimentation:

The art of determining the dosage of a therapeutic by analyzing the presence of polymorphisms is highly unpredictable. The total number of polymorphisms in the genome of an individual and the significance of each of these polymorphisms is highly variable and unpredictable. The specification relies on the knowledge in the prior art of known mutations in genes that are associated with a disease and which the art teaches are associated with providing a protective effect by converting harmful oxygen molecules into less reactive oxygen molecules. The specification also relies on the teachings in the prior art that antioxidant compounds can be used as a means to provide a protective effect against oxidative damage. Based on this knowledge in the prior art, the specification proposes a method by which one can determine the dosage of an antioxidant by calculating the number of polymorphisms in SOD and catalase

genes of an individual. However, the specification teaches only the general concept of increasing the dosage of an antioxidant based on the number of polymorphisms. Yet, it is highly unpredictable as to what would be the effect of increasing dosages of an antioxidant on the treatment or prevention of disease relative to the number of polymorphisms. There are no teachings in the specification which show the effect of antioxidant dosage on treatment. There are also no teachings in the specification as to the effect of the number of mutations in SOD and catalase on the occurrence of disease. It is highly unpredictable as to what would constitute an appropriate "increased dosage." For particular antioxidants, such as Vitamin E, the recommended daily allowance (RDA) is well known in the art. It is unclear as to whether the RDA is to be used as the starting point for increasing the dosage, or whether some other unspecified quantity of antioxidant is to be used as the starting dosage. There are no teachings in the specification or prior art of a positive effect associated with increasing the dosage of the antioxidant above the RDA. Thereby, it is highly unpredictable as to whether increasing the dosage incrementally with each polymorphism will effect response to the antioxidant treatment.

The teachings of Forsberg (Archives Biochem Biophysics. May 2001. 389: 84-93; previously cited) support the unpredictability of establishing an association between a polymorphism and a disorder at the time the invention was made. Specifically, Forsberg (pages 90-91) states that "These are early days for using a genetic epidemiological approach to the study of oxidative stress-related disease. As has been the case for other association studies, it is expected that positive studies will be contrasted with

negative results. Therefore large-scale genotyping methods and carefully selected populations will be required to generate reliable data...Human genome and comprehensive polymorphism data will become available shortly, determination of phenotypes will proceed more slowly, but eventually a global approach where many carefully characterized genetic variants queried in disease association studies is an achievable goal."

Amount of Direction or Guidance Provided by the Specification:

The specification does not provide sufficient guidance to enable the skilled artisan to select an appropriate increased dosage of antioxidant composition based on the presence of polymorphisms in SOD and catalase genes. The specification does not teach the baseline dosage and does not teach what degree of increase in an antioxidant would be required for each polymorphism. For instance, is the dosage doubled relative to a control individual that does not have that particular polymorphism? If so, is it at all relevant that the control individual may have another polymorphism that is more tightly correlated with the disorder and has multiple polymorphisms that are absent from the test individual? While the specification teaches that weighing factors may be assigned to the polymorphisms, how are these weighing factors taken together to determine the appropriate increase in dosage? The claims do not include any of this information and these teachings are not provided in the specification. Rather, the claims generically state that for each occurrence of any polymorphism in a SOD or catalase gene, the dosage of the antioxidant should be increased. Yet, in circumstances in which the polymorphism is not tightly linked to the disease and/or does not directly or indirectly

affect oxidation, it is unclear as to how increasing the dosage will effect the outcome of treatment. Many polymorphisms may be "associated" with an increased risk of susceptibility to a disease, but do not necessarily have an effect on an individual's phenotype. The specification does not provide sufficient guidance as to how to select which of the multitude of possible polymorphisms in the SOD and CAT genes could be detected, added up and used to determine the quantity of the increase in dosage of an antioxidant that should be administered to a patient.

There are no teachings in the specification regarding the effect of increasing the dosage of an antioxidant based on the total number of polymorphisms present in an individual's SOD and catalase genes on treatment outcome or prevention of a disease. The concepts that mutations in antioxidant enzymes increase susceptibility to disease and that a diet rich in antioxidants decreases susceptibility to disease were known in the art at the time the invention was made. For instance, with respect to breast cancer, Ambrosone (Cancer Research. 1999. 59: 602-606; see abstract) states that "The finding that risk was greatest among women who consumed lower amounts of dietary antioxidants and was minimal among high consumers indicates that a diet rich in sources of antioxidants may minimize the deleterious effects of the MnSOD polymorphism, thereby supporting public health recommendations for the consumption of diets rich in fruits and vegetables as a preventative measure against cancer." However, the present invention is not limited to methods of determining whether to administer an antioxidant to a patient based on the presence of a mutation in a SOD or CAT gene. Rather, the claims require determining an appropriate dosage of any

antioxidant used to treat any disorder, wherein the dosage is increased based on each occurrence of the polymorphisms of a C to T at -262 of the catalase gene and a val7glu polymorphism in CuZnSOD. The specification does not provide sufficient guidance for selecting a dosage of any anti-oxidant to treat any disease based on the number of said polymorphisms. Further, the specification has not identified a sufficient number of polymorphisms in the catalase and superoxide dismutase genes, or of any oxidative damage associated polymorphisms in any genes that are correlated with the occurrence of any pathology involving oxidative damage to humans.

Regarding claim 110, the specification does not provide sufficient guidance as to how one would calculate a susceptibility factor. The specification (para [0044]) states that :

"Occurrence of every disorder-associated polymorphisms in a gene related to oxidative stress is not necessarily equally indicative of susceptibility to oxidative stress. In order to account for differences in the significance of various disorder-associated polymorphisms, a weighting factor can be assigned to each polymorphism detected in the methods and kits described herein. As indicated above, four genes (MnSOD, CZSOD, CAT, and GP) are known to have very significant roles in oxidative stress in humans. All else being equal, disorder-associated polymorphisms that occur in one of these four genes are more significant than polymorphisms that occur in genes having less significant roles in oxidative stress. Thus, a greater weighting factor can be assigned to these polymorphisms than to others. By way of example, the weighting factor assigned to these four polymorphisms can be 1 to 10 times greater than the weighting factor assigned to disorder- associated polymorphisms (having equal correlation with the corresponding disorder, as discussed below) in other genes."

Thereby, the specification clearly acknowledged that different polymorphisms will have varying effects on the occurrence of a pathology. However, the specification does not provide specific guidance as to the particular weighting factor that should be

assigned to a CuZnSOD polymorphism, a catalase polymorphism, or any of the millions of other possible polymorphisms encompassed by the claims.

Similarly, regarding the different pathologies encompassed by the claims, the specification (para [0045]) acknowledges that:

Another factor which can influence the significance that is assigned to occurrence of a disorder-associated polymorphism in a human's genome is the degree to which the polymorphism is correlated with the corresponding disorder. Some disorders are highly correlated with occurrence of a genetic polymorphism, and other disorders exhibit lower correlation with a polymorphism.

However, the specification does not identify particular disorders that are highly correlated or exhibit a lower correlation with particular polymorphisms. Rather, the specification indicates that one can perform additional research to try to determine the degree to which a polymorphism is associated with a particular pathology. The results of such research are highly unpredictable and thereby constitute undue experimentation.

Conclusions:

Case law has established that '(t)o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *In re Wright* 990 F.2d 1557, 1561. *In re Fisher,* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) it was determined that '(t)he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art". The amount of

guidance needed to enable the invention is related to the amount of knowledge in the art as well as the predictability in the art. Furthermore, the Court in *Genetech Inc. v Novo Nordisk* 42 USPQ2d 1001 held that '(I)t is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of the invention in order to constitute adequate enablement". In the instant case, the novel aspects of the invention are not adequately disclosed because the specification does not teach how one can use the information regarding the number of CuZnSOD and catalase polymorphisms to determine the appropriate dosage of any anti-oxidant treatment. The specification does not provide sufficient guidance as to how to interpret the information regarding the number and identity of polymorphisms to determine an appropriate dosage. Further, the specification does not teach an association between an increase antioxidant dosage and effectiveness of treating or preventing disease or a general association between the total number of polymorphisms and oxidative damage. Moreover, the specification does not teach, or provide sufficient guidance to identify without undue experimentation, a representative number of polymorphisms in the catalase and superoxide dismutase genes, or a representative number of any “oxidative damage-associated polymorphisms” in any genes that are correlated with the occurrence of any pathology involving oxidative damage to humans. Accordingly, although the level of skill in the art of molecular biology is high, given the lack of disclosure in the specification and in the prior art and the unpredictability of the art, it would require undue experimentation for one of skill in the art to make and use the invention as claimed.

RESPONSE TO ARGUMENTS:

In the response, Applicants state that a 132 Declaration is provided stating that one of skill in the art would know how to determine or could determine without undue experimentation a sequence of a superoxide dismutase or a sequence of a catalase gene, and could determine if a polymorphism is associated with a pathology.

The 132 Declaration is executed by Robert Ricciardi, co-inventor and Chief Science Officer of GeneLink, the assignee of the present application (see the reply filed May 16, 2007).

The 132 Declaration states that it is the opinion of the declarant that one of skill in the art would know how to obtain a sequence for a gene encoding a superoxide dismutase and a gene encoding a catalase, by e.g., going to the NCBI database web site. It is stated that the NCBI web site also provides information regarding the occurrence of SNPs. The declaration states that "It is my opinion that one skilled in the art would know how to determine if a polymorphism in a human gene encoding a superoxide dismutase and a human gene encoding a catalase has been identified as associated with a pathology." Kimura, Alexander and Jiang are cited in the declaration as teaching polymorphisms associated with disorders. The declaration goes on to state that one could search for additional polymorphisms and determine if they have been associated with a disorder.

The 132 declaration has been fully considered but is not persuasive because the declaration is a statement of opinion and does not contain any evidence to support these opinions. Further, the declaration does not address, and thereby does not establish the enablement of, the basic concept of the claims which requires determining

a dosage of an anti-oxidant by assessing the number of polymorphisms of the C to T polymorphism at position -262 of a catalase gene and the polymorphism resulting in a val7glu substitution at amino acid 7 of CuZn SOD. While databases exist which list polymorphisms and gene sequences, these databases do not apprise one of how to select an appropriate dosage of any anti-oxidant to treat any disease based on the number of polymorphisms of a C to T at -262 of a catalase gene and a polymorphism resulting in a val7glu substitution at amino acid 7 of CuZn SOD. Further, these databases do not provide guidance as to how to select weighting values or susceptibility values to determine the degree to which a polymorphism is correlated with a disorder and thereby to calculate the relative susceptibility of a human to any oxidative-damage associated disorder by determining the number of polymorphisms.

Regarding the Alexander and Jiang references, copies of these references were not provided and thereby have not been considered by the examiner. Further, regarding the Alexander reference, this reference was published after the filing date of the present invention. Thereby, the Alexander reference does not provide evidence that the claimed invention was enabled at the time the invention was made.

Regarding the Kimura reference, this reference teaches an association between a val/ala polymorphism in the MnSOD gene and the occurrence of age-related macular degeneration. However, the present claims are not directed to a method of detecting a polymorphism in the MnSOD gene, or a method for determining an association between a val/ala polymorphism in the MnSOD gene and the occurrence of age-related macular degeneration. Kimura does not establish the unpredictability of determining a dose of any anti-oxidant by determining the number of the claimed catalase and CuZnSOD polymorphisms, or of determining which of the multitude of possible diseases are correlated with the occurrence of the claimed catalase and CuZnSOD polymorphisms.

Further, the teachings of Kimura support the unpredictability in the art in that Kimura found that polymorphisms in the cytochrome P-450 IAI, glutathione S-transferase and microsomal epoxide hydrolase genes were not correlated with age-related macular degeneration. Thereby, it is unpredictable as to which of the possible polymorphisms encompassed by the claims will be correlated with particular conditions involving oxidative damage.

New Grounds of Rejection

Claim Rejections - 35 USC § 101

6. 35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and
requirements of this title.

Claims 105 and 110-112 are rejected under 35 U.S.C. 101 because the claims are directed to non statutory subject matter. The claims are drawn to methods for selecting a dose of an antioxidant. However, the methods as claimed do not produce any physical transformation or produce a tangible result. The claims encompass performing only mental steps, i.e. assessing the occurrence of polymorphisms in the catalase and Cu/Zn SOD genes. Claim 110 further includes the mental step of calculating a susceptibility value by summing the number of polymorphisms or assigning a weighting factor to a polymorphism and then summing the number of polymorphisms. The claims do not recite active process steps whereby the information obtained regarding the occurrence of a polymorphism is used to achieve the result of selecting a dose of an antioxidant. Thus, the steps of assessing the occurrence of a

polymorphism and calculating a susceptibility value by summing the number of polymorphisms or assigning a weighting factor to a polymorphism and then summing the number of polymorphisms does not produce any physical transformation since the claims do not result in the transformation of an article “to a different state or thing.” Further, the claims do not require the use of a particular machine to accomplish the steps of accessing a polymorphism or selecting a dose of an antioxidant.

The courts have stated that "While a scientific truth, or the mathematical expression of it, is not patentable invention, a novel and useful structure created with the aid of knowledge of scientific truth may be."; Warmerdam, 33 F.3d at 1360, 31 USPQ2d at 1759 ("steps of locating 'a medial axis, and creating' a bubble hierarchy.., describe nothing more than the manipulation of basic mathematical constructs, the paradigmatic abstract idea'") (see MPEP § 2106 IV).

The Courts have also stated that manipulation of abstract concepts or ideas constitute non-statutory subject matter. If the "acts" of a claimed process manipulate only numbers, abstract concepts or ideas, or signals representing any of the foregoing, the acts are not being applied to appropriate subject matter. Schrader, 22 F.3d at 294-95, 30 USPQ2d at 1458-59. Thus, a process consisting solely of mathematical operations, i.e., converting one set of numbers into another set of numbers, does not manipulate appropriate subject matter and thus cannot constitute a statutory process. In practical terms, claims define nonstatutory processes if they:

-- consist solely of mathematical operations without some claimed practical (i.e., executing a "mathematical algorithm;"); or

-- simply manipulate abstract ideas, e.g. a bid (Schrader, 22 F.3d at 293-94,30 USPQ2d at 1458-59) or a bubble hierarchy (Warmerdam, 33 F.3d at 1360, 31 USPQ2d at 1759), without some claimed practical application.
(see MPEP § 2106 IV (B) (1)).

It is further noted that In re Schrader states: "the grouping or regrouping of bids cannot constitute a physical change, effect or result".. "The only physical effect or result which is required by the claim is the entering of bids in a "record," a step that can be accomplished simply by writing the bids on a piece of paper or chalkboard. For purposes of Section 101, such activity is indistinguishable from the data gathering steps which we said in In re Grams, 888 F.2d 835, 12 USPQ 2d 1924 (Fed. Cir. 1989), were insufficient to impart patentability to a claimed involving the solving of a mathematical algorithm". Therefore, the courts have stated that identifying without physical manipulation, is indistinguishable from data gathering and is insufficient to impart patentability.

Claim Rejections - 35 USC § 112 – New Matter

7. Claims 105 and 110-112 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The specification as originally filed does not provide support for the recitation in the claims that the increased susceptibility to a pathology is relative to a human with fewer oxidative damage-associated polymorphisms.

The response of April 30, 2007 points to paras [0019], [0041], [0044] and [0047] as providing support for amendments to the claims. However, the cited passages do not provide support for this concept. In particular, para [0041] teaches only that susceptibility can be calculated relative to a hypothetical human "whose genome does not contain a single disorder-associated polymorphism in a gene associated with oxidative stress. Alternatively susceptibility can be calculated relative to another human who may have one or more different disorder-associated polymorphism than the human being accessed." These teachings do not provide support for the distinct concept that susceptibility is relative "to a human with fewer" oxidative damage-associated polymorphisms.

Regarding claim 110, the specification as originally filed does not appear to provide support for the recitation in this new claim of "calculating a susceptibility value for the condition by either summing the identified polymorphisms to yield a value for the human, or assigning a weighting factor to each polymorphism and then summing the weighting factors to yield a value for the human, wherein a value for the human greater than zero indicates a greater susceptibility to the oxidative stress condition for the human."

The cited passages do not provide support for this amendment. In particular, para [0044] teaches assigning a weighting factor to a polymorphism. Para [0047] teaches that:

> An overall oxidative stress susceptibility score for a human can be determined as follows. A significance score can be assigned to each disorder-associated polymorphism that is detected in the human's genome using a method or kit described herein. The significance score is a constant (e.g., 1.00), and is multiplied by any significance factor (e.g., 1-10, preferably 2, for the MnSOD, CZSOD, CAT, and GP genes) and by any correlation factor that is available. If information is available which describes the correlation between homozygosity for the polymorphism and the corresponding disorder, then that correlation factor should be used in place of the correlation factor for mere occurrence of the polymorphism, at least if the method or kit is used to rule out occurrence in the subject's genome of corresponding non-disorder- associated polymorphisms. If significance and correlation factors are not available, then values of 1.00 should be assigned to each. An overall score is determined by summing the significance score for each disorder-associated polymorphism that is detected using the method or kit. This overall oxidative stress susceptibility score can be compared with the values obtained from other subjects, or it can be compared with the value (i.e., zero) which would be expected to occur in a human whose genome does not include any disorder-associated polymorphism in a gene associated with oxidative stress.

Accordingly, the specification discusses the concepts of assigning a weighting factor to a polymorphism and summing a significance score. However, these teachings do not provide support for the distinct concept of summing the polymorphisms to yield any "value" or assigning a weighting factor to each polymorphism and summing the weighting factors to yield a "value", wherein a value greater than zero indicates a greater susceptibility to any oxidative stress condition.

Claim Rejections - 35 USC § 112 second paragraph

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 105 and 110-112 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 105 and 110-112 are indefinite because the claims do not recite a clear nexus between the preamble of the claims and the final process steps of the claims. The claims are drawn to a method of selecting a dose of an anti-oxidant. However, the claims recite only a step of assessing the occurrence of a polymorphism. Thereby, the claims omit essential process steps that are required to accomplish the objective set forth in the preamble of the claims of selecting the dose of an anti-oxidant.

Double Patenting

9. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

10. The following grounds of rejection are newly added and necessitated by Applicant's filing of new applications subsequent to the prior Office action.

11. Claims 105 and 110-112 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 98 of copending Application No. 11/931,447. Although the conflicting claims are not identical, they are not patentably distinct from each other because both the present claims and the claims of '447 are inclusive of methods for selecting a dose of an anti-oxidant by assaying for a C to T polymorphism at position -262 of the catalase gene and a polymorphism resulting in a valine to glutamic acid at amino acid position 7 of CZSOD. With respect to claim 110, while the claims of '447 do not specifically recite a step of summing the identified polymorphisms, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have determined the sum of the polymorphisms since the claims of '447 require that each occurrence of a polymorphism indicates an increased risk of susceptibility to a pathology associated with oxidative stress. Thereby, determining the total number of the polymorphisms would have provided the advantage of determining the degree of an increased susceptibility to a pathology associated with oxidative damage.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

12. Claims 105 and 110-112 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 32 and 48 of copending Application No. 11/731,180. Although the conflicting claims are not identical,

they are not patentably distinct from each other because both the present claims and the claims of '180 are inclusive of methods for selecting a dose of an anti-oxidant by assaying for a polymorphism in the catalase gene and a polymorphism in the CZSOD gene. The claims of '180 differ from the present claims in that the claims of '180 are limited to methods for selecting the dose of a skin protective agent, whereas the present claims are generic to selecting a dose of any anti-oxidant composition. However, skin protective agents are encompassed by anti-oxidant compositions and thereby the present claims are generic to the species recited in the claims of '180. Further, the claims of '180 do not recite a particular polymorphism in the catalase and CZSOD genes. However, when read in light of the specification of '180, it is clear that the recited polymorphism associated with a dose of an agent is intended to specifically include the presently claimed polymorphisms of a thymine at position -262 of the catalase gene and a polymorphism resulting in a glutamic acid at amino acid position 7 of CZSOD. With respect to claim 110, while the claims of '180 do not specifically recite a step of summing the identified polymorphisms, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have determined the sum of the polymorphisms since the claims of '180 require that each occurrence of a polymorphism indicates an increased risk of susceptibility to a pathology associated with oxidative stress. Thereby, determining the total number of the polymorphisms would have provided the advantage of determining the degree of an increased susceptibility to a pathology associated with oxidative damage.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is 571-272-0747. The examiner can normally be reached on Monday-Thursday (6:30-5:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Carla Myers/
Primary Examiner, Art Unit 1634